Complete Summary

GUIDELINE TITLE

Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines.

BIBLIOGRAPHIC SOURCE(S)

American Society of Clinical Oncology. Recommendations for the use of antiemetics: Evidence-based, clinical practice guidelines . J Clin Oncol 1999 Sep;17(9):2971. [277 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Nausea and vomiting associated with chemotherapy and radiotherapy for cancer.

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Oncology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To develop recommendations regarding antiemetic therapy.

TARGET POPULATION

Adult and pediatric patients with cancer receiving chemotherapy or radiation therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Antiemetic pharmacotherapy for prevention and treatment of chemotherapy-induced emesis (acute, delayed and anticipatory) and radiation-induced emesis:

- Agents with the highest therapeutic index, including
  - serotonin (5-hydroxytryptamine [5-HT_3]) receptor antagonists (dolasetron [Anzemet], granisetron [Kytril], ondansetron [Zofran], tropisetron [Navoban], and
  - corticosteroids (dexamethasone [Decadron], methylprednisolone [Medrol])
- Agents of lower therapeutic index, including
  - dopamine antagonists (metoclopramide [Reglan], prochlorperazine [Compazine]),
  - butyrophenones, phenothiazines, and cannabinoids
- Adjunctive drugs, including benzodiazepines and antihistamines
- Combinations of antiemetics: serotonin antagonists with corticosteroids

MAJOR OUTCOMES CONSIDERED

- Control of emesis (vomiting), usually monitored by counting the number of vomiting episodes
- Control of nausea (perception that emesis may occur), as judged by the patient and measured by questionnaire

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Pertinent information from the published literature as of July 1998 was retrieved and reviewed for the creation of these guidelines. MEDLINE (National Library of Medicine, Bethesda, MD) and other databases were searched for pertinent articles. The following keywords or phrases were used: antiemetics, neoplasms, adverse effects, anticipatory + nausea, anticipatory + vomiting, serotonin antagonists, phenothiazines, butyrophenones, cannabinoids, corticosteroids, and metoclopramide. Directed searches were made of the primary articles.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

I. Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials have low false-positive and low false-negative errors (high power)
II. Evidence obtained from at least one well-designed experimental study. Randomized trials have high false-positive and/or false-negative errors (low power)
III. Evidence obtained from well-designed, quasi-experimental studies, such as non-randomized, controlled, single-group, pre-post, cohort, time, or matched case-control series
IV. Evidence from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies
V. Evidence from case reports and clinical examples

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The Panel identified topics to be addressed by the guidelines, developed a strategy for completion of the guidelines, and reviewed the literature. The Panel emphasized the inclusion of prospective random-assignment studies. Phase II trials and clinical reports that evaluated less-well-studied areas of antiemetic treatment were also reviewed. The recommendations made by the Expert Panel are based on current methods of emetic treatment and prevention.

The Panel did not attempt to codify established practice. The experts reviewed the available evidence and added their best clinical judgment to make final recommendations, using standardized language to characterize the strength of the evidence. In accordance with the ASCO Health Services Research Policies and Procedures for guidelines, "recommendation" was used when there was level I or II evidence and Panel consensus. "Suggestion" was used when there was level III, IV, or V evidence and Panel consensus. "No guideline possible" was used when there were no data or the Panel could not reach consensus.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Consensus Development Based on Evidence

The Panel identified topics to be addressed by the guidelines, developed a strategy for completion of the guidelines, and reviewed the literature. The Panel emphasized the inclusion of prospective random-assignment studies. Phase II trials and clinical reports that evaluated less-well-studied areas of antiemetic treatment were also reviewed. The recommendations made by the Expert Panel are based on current methods of emetic treatment and prevention. The guidelines were circulated in draft form through several iterations, and all members of the Panel had opportunities to comment on the recommendations.

The Panel did not attempt to codify established practice. The experts reviewed the available evidence and added their best clinical judgment to make final recommendations, using standardized language to characterize the strength of the evidence. In accordance with the ASCO Health Services Research Policies and Procedures for guidelines, "recommendation" was used when there was level I or II evidence and Panel consensus. "Suggestion" was used when there was level III, IV, or V evidence and Panel consensus. "No guideline possible" was used when there were no data or the Panel could not reach consensus.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grade of Recommendation

There is evidence of type 1 or consistent findings from multiple studies of type II, III, or IV

There is evidence of type II, III, or IV and findings are generally consistent

There is evidence of type II, III, or IV but findings are inconsistent

There is little or no systematic empirical evidence

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The content of the guidelines and the manuscript were reviewed and approved by the Health Services Research Committee and by the ASCO Board before dissemination. In addition, several practitioners among the ASCO membership

who had not been directly involved in development of the guidelines were asked to assess the clarity and utility of the document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (I-V) and grades of evidence (A-D, NG) for recommendations are defined at the end of the Major Recommendation field.

I. Chemotherapy-Induced Emesis
  A. Acute Emesis (vomiting occurring 0 to 24 hours after chemotherapy)
    1. Antiemetic Agents: Highest Therapeutic Index
      a. Serotonin Receptor Antagonists
        i. Agent equivalence

Guideline: At equivalent doses, serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably based on convenience, availability, and cost.

Level of Evidence: I

Grade of Recommendation: A

        ii. Drug dosage

Guideline: >Established, proven doses of all agents are recommended.

Level of Evidence: I

Grade of Recommendation: A

        iii. Drug schedule

Guideline: Single doses of antiemetics are effective and preferred for convenience and cost.

Level of Evidence: I

Grade of Recommendation: A

        iv. Route of administration

Guideline: At biologically equivalent doses, oral agents are equally effective and are as safe as intravenous antiemetics. In most settings, oral agents are less costly and more convenient; for

these reasons, they are recommended over intravenous therapy.

Level of Evidence: I

Grade of Recommendation: A

b. Corticosteroids

i. Agent equivalence and route of administration

Guideline: At equivalent doses, corticosteroids have equivalent safety and efficacy and can be used interchangeably.

Level of Evidence: IV and Expert Consensus

Grade of Recommendation: C

ii. Drug dose and schedule

Guideline: Single doses of corticosteroids are recommended.

Level of Evidence: II

Grade of Recommendation: B

2. Antiemetic Agents: Lower Therapeutic Index - Dopamine Antagonists, Butyrophenones, Phenothiazines, and Cannabinoids

Guideline: For chemotherapy with a high risk of emesis, selective serotonin antagonists (with dexamethasone) are recommended.

Level of Evidence: I

Grade of Recommendation: A

3. Antiemetic Agents: Adjunctive Drugs - Benzodiazepines and Antihistamines

Guideline: Benzodiazepines and antihistamines are useful adjuncts to antiemetic drugs but are not recommended as single agents.

Level of Evidence: II

Grade of Recommendation: B

4. Antiemetic Agents: Combinations of Antiemetics

Guideline: It is recommended that serotonin antagonists be given with corticosteroids.

Level of Evidence: I

Grade of Recommendation: A

5. Risk Factors for Acute Emesis
   a. Patient Characteristics
   b. Chemotherapeutic Agents
   c. Guidelines
      i. (a) High risk: Cisplatin

Guideline: The combination of a 5-HT_3 antagonist plus a corticosteroid is recommended before chemotherapy.

Level of Evidence: I

Grade of Recommendation: A

      ii. (b) High risk: noncisplatin

Guideline: The combination of a 5-HT_3 antagonist plus a corticosteroid is recommended before chemotherapy.

Level of Evidence: I, II, III, and Expert Consensus

Grade of Recommendation: A-B

      iii. Intermediate risk

Guideline: A corticosteroid is suggested for patients being treated with agents of intermediate emetic risk.

Level of Evidence: III, IV, and Expert Consensus

Grade of Recommendation: B, D

      iv. Low risk:

Guideline: It is suggested that for patients being treated with agents of low emetic risk, no antiemetic be routinely administered before chemotherapy.

Level of Evidence: V and Expert Consensus

Grade of Recommendation: D

v. Combination chemotherapy

Guideline: It is suggested, that when combination chemotherapy is given, the patient be given antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk.

Level of Evidence: IV

Grade of Recommendation: D

vi. Multiple consecutive days of chemotherapy

Guideline: It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy.

Level of Evidence: II and III

Grade of Recommendation: B

B. Delayed Emesis (vomiting occurring >24 hours after chemotherapy)
   1. Antiemetic Agents
      a. Single Agents
         i. Corticosteroids
         ii. Metoclopramide and serotonin receptor antagonists
      b. Combinations of Agents
   2. Risk Factors for Delayed Emesis
      a. Patient Characteristics
      b. Chemotherapeutic Agents
      c. Guidelines
         i. (a) High risk: cisplatin

Guideline: For all patients receiving cisplatin, a corticosteroid plus metoclopramide or plus a 5-HT_3 antagonist is recommended for the prevention of delayed emesis.

Level of Evidence: I

Grade of Recommendation: A

ii. (b) High risk: noncisplatin

Guideline: A prophylactic corticosteroid as a single agent, a prophylactic corticosteroid plus metoclopramide, and a prophylactic corticosteroid plus a 5-HT_3 antagonist are regimens suggested for the prevention of delayed emesis.

Level of Evidence: III - V

Grade of Recommendation: B-D

iii. Intermediate- to low-risk

Guideline: No regular preventive use of antiemetics for delayed emesis is suggested for patients receiving these chemotherapeutic agents.

Level of Evidence: V and Expert Consensus

Grade of Recommendation: D

C. Anticipatory Emesis

1. Prevention

Guideline: Use of the most active antiemetic regimens appropriate for the chemotherapy being given to prevent acute or delayed emesis is suggested. Such regimens must be used with the initial hemotherapy, rather than after assessment of the patient's emetic response to less effective treatment.

Level of Evidence: III

Grade of Recommendation: D

2. Treatment

Guideline: If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and is suggested (Hallowfield, 1992; Morrow & Morrell, 1982; Morrow et al., 1992; Morrow, 1986; Redd & Andrykowski, 1982; Redd et al., 1987; Burish & Lyles, 1979; Burish et al., 1987; Burish & Tope, 1992).

Level of Evidence: III

Grade of Recommendation: B

D. Special Emetic Problems

1. Emesis in Pediatric Oncology

Guideline: The combination of a 5-HT_3 antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high emetic risk.

Level of Evidence: III

Grade of Recommendation: B

2. High-Dose Chemotherapy

Guideline: A 5-HT_3 antagonist plus a corticosteroid is suggested.

Level of Evidence: II and III

Grade of Recommendation: C

3. Vomiting and Nausea Despite Optimal Prophylaxis in Current or Prior Cycles

Guideline: It is suggested that clinicians (1) conduct a careful evaluation of risk, antiemetic, chemotherapy, tumor, and concurrent disease and medication factors, (2) ascertain that the best regimen is being given for the emetic setting, (3) consider adding an antianxiety agent to the regimen, and (4) consider substituting a dopamine receptor antagonist, such as high-dose metoclopramide, for the 5-HT_3 antagonist (or add the dopamine antagonist to the regimen).

Level of Evidence: V and Panel Consensus

Grade of Recommendation: D and Panel Consensus

II. Radiation-Induced Emesis

A. Risk Factors for Radiation-Induced Emesis

1. Guidelines

a. High Risk: Total Body Irradiation

Guideline: A serotonin receptor antagonist should be given with or without a corticosteroid before each fraction and for at least 24 hours after.

Level of Evidence: II and III

Grade of Recommendation: B and C

b. Intermediate Risk: Hemibody Irradiation, Upper Abdomen, Abdominal-Pelvic, Mantle, Cranial Radiosurgery, and Craniospinal Radiotherapy

Guideline: A serotonin receptor antagonist or a dopamine receptor antagonist should be given before each fraction.

Level of Evidence: II and III

Grade of Recommendation: B

c. Low Risk: Radiation of the Cranium Only, Breast, Head and Neck, Extremities, Pelvis, and Thorax

Guideline: Treatment should be given on an as-needed basis only. Dopamine or serotonin receptor antagonists are advised. Antiemetics should be continued prophylactically for each remaining radiation treatment day.

Level of Evidence: IV and V

Grade of Recommendation: B-D

Definitions

Type of Evidence for Recommendation

Level I: Evidence obtained from meta-analysis of multiple well-designed controlled studies; randomized trials with low false-positive and low false-negative errors (high power)

Level II: Evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and/or negative errors (low power)

Level III: Evidence obtained from well-designed quasi-experimental studies, such as nonrandomized controlled single-group pre-post, cohort, time or matched case-control series

Level IV: Evidence from well-designed nonexperimental studies, such as comparative and correlation descriptive and case studies

Level V: Evidence from case reports and clinical examples

Grade of Evidence for Recommendation

Category A: There is evidence of type I or consistent findings from multiple studies of types II, III, or IV

Category B: There is evidence of types II, III, or IV and findings are generally consistent

Category C: There is evidence of types II, III, or IV, but findings are inconsistent

Category D: There is little or no systematic empirical evidence

Category NG: Grade not given

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Chemotherapy-induced emesis

Overall. With currently available agents, complete control of emesis, i.e., no vomiting, is achievable in the majority of patients in the first 24 hours and in approximately 45% of patients during the first 5 to 7 days of chemotherapy.

Complete control of vomiting correlates highly with patients' perception of emesis and with patients' satisfaction with their emetic control. Many large random-assignment trials have shown that complete control rates for vomiting are higher than those for the complete control of nausea.

Acute emesis

High risk of emesis - cisplatin. Large, multicenter, randomized trials have shown the rate of complete control of acute emesis (occurring in the first 24 hours) to be approximately 75% (range, 58% to 96%), after high-dose cisplatin using the recommended regimen (i.e., serotonin receptor antagonist plus a corticosteroid prophylactically).

High risk of emesis - noncisplatin. In instances where there is level I data for noncisplatin agents with a high emetic potential (cyclophosphamide, the anthracyclines, and combinations of these agents), several large, randomized, multicenter trials have documented 85% to 90% complete control of acute emesis using the recommended regimen (i.e., serotonin receptor antagonist plus a corticosteroid prophylactically). A lower level of evidence has been demonstrated for agents such as dacarbazine.

Intermediate risk. For patients receiving an agent of intermediate emetic risk, the Panel agreed that the complete control rate should exceed 90% with the use of a single dose of corticosteroid. There is no formal documentation of efficacy with antiemetic treatments for these lower-risk chemotherapy agents.

Low risk. For patients receiving an agent of low emetic risk and for whom the decision is made to give an antiemetic, antiemetic control should exceed 95% according to agreement among Panelists.

Delayed emesis

High risk - cisplatin. Trials indicate that a corticosteroid plus metoclopramide or a 5-HT_3 antagonist can give rates of complete control of delayed emesis in the range of 50% to more than 70%, compared with only 11% to 30% control without antiemetic. A large, multi-center randomized trial obtained equivalent rates of control with corticosteroids plus either metoclopramide or ondansetron, showing that either regimen could be given.

Radiation-induced emesis

High risk of emesis: Total Body Irradiation (TBI). Complete control rates with 5-HT_3 antagonists for TBI vary between 50% and 90%. The role of corticosteroids in combination with 5-HT_3 antagonists has not been studied. Some panelists advised giving corticosteroids to patients receiving TBI because of the marked risk in this situation and findings in preliminary reports.

Intermediate risk: Hemibody irradiation, upper abdomen, abdominal-pelvic, mantle, craniospinal irradiation, and cranial radiosurgery. Existing evidence suggests that preventative treatment is better than intervention on an as-needed basis. There is some evidence to suggest that in fractionated radiotherapy, the efficacy of 5-HT_3 antagonists may decrease after the first week of treatment, making it difficult to suggest what the optimal duration of prophylactic treatment should be. Trials indicate that both serotonin and dopamine receptor antagonist agents are effective for patients who require treatment in this group, with most studies indicating better control with serotonin receptor antagonists.

POTENTIAL HARMS

Serotonin receptor antagonists (5-HT_3). These agents share the same low side effect pattern, with mild headache, transient asymptomatic transaminase elevations, and constipation being among the most commonly reported adverse events.

Single-dose corticosteroids. Side effects are rare, although elevations of serum glucose levels and sleep disturbances occur.

Dopamine antagonists. Side effects include acute dystonic reactions, akathisia, and sedation.

Subgroups Most Likely to be Harmed:

Dopamine antagonists. When given over several consecutive days, dopamine antagonists cause a high incidence of dystonic reactions and are not a good choice for general multiple-day use in the pediatric population.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. They cannot be considered to be inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.
- It is also important to note that not all relevant questions regarding emesis in cancer care have been addressed by clinical trials. The antiemetic methods listed in this guideline have been shown to be beneficial (or not), but additional research in the prevention of emesis is strongly encouraged. In some instances, specific areas of research need are indicated in this guideline. As ongoing research is completed, helpful results from these trials will be incorporated into updates of these guidelines.
- ASCO considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative and novel therapies for this symptom in which better treatment is of paramount importance. In that guideline development involves a review and synthesis of the latest literature, practice guidelines also serve to identify important questions for further research and those settings in which investigational therapy should be considered.
- Due to a lack of systematic evaluation, controversy exists concerning definitions of emetic risk groups for patients receiving radiotherapy. It is the identification of these risks groups that indicates whether antiemetic therapy should be given routinely on a preventative basis or whether they should be reserved for treatment as needed by individual patients. The radiation oncology literature indicates that treatment field is one of the major determinants of emetic risk. Dose of radiotherapy administered per fraction and the pattern of fractionation are more difficult to define but are important considerations for risk. The Panel reached consensus on definitions of radiotherapy-induced emesis risk groups.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

American Society of Clinical Oncology. Recommendations for the use of antiemetics: Evidence-based, clinical practice guidelines . J Clin Oncol 1999 Sep;17(9):2971. [277 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Sep

GUIDELINE DEVELOPER(S)

American Society of Clinical Oncology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Society of Clinical Oncology

GUIDELINE COMMITTEE

ASCO Antiemetic Guideline Expert Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The Panel was composed of experts in clinical medicine, clinical research, outcomes/health services research, medical decision-making, and health economics, with a focus on expertise in supportive care and in antiemetics. A patient representative was also included on the Panel. Clinical experts represented all relevant disciplines, including medical oncology, oncology nursing, radiation oncology, pediatric oncology and oncologic pharmacy practice.

Members: Richard J. Gralla, MD (Co-chair); David Osoba, MD (Co-chair); Mark G. Kris, MD; Peter Kirkbride, MD; Paul J. Hesketh; Lawrence W. Chinnery; Rebecca Clark-Snow, RN, BSN, OCN; David P. Gill, MD; Susan Groshen, PhD; Steven Grunberg, MD; James M. Koeller, MD; Gary R. Morrow, PhD; Edith A. Perez, MD; and Jeffrey H. Silber, MD, PhD; David G. Pfister, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All participants in the guideline development process complied with the American Society of Clinical Oncology (ASCO) policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict.

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society of Clinical Oncology (ASCO) Web site.

Print copies: Available from American Society of Clinical Oncology, Health Services Research, 1900 Duke Street, Suite 200, Alexandria, VA 22314.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

A document titled "A Patient's Guide: Preventing and Treating Nausea and Vomiting Caused by Cancer Treatment" is available from the American Society for Clinical Oncology (ASCO).

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on January 3, 2000. It was verified by the guideline developer on January 18, 2000.

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